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Regarding the amendments, inadvertently, the numbering of the new claims introduced by the second preliminary amendment did not follow consecutively from the numbering of the claims introduced by the earlier preliminary amendment. Therefore, Applicants have canceled all of the claims and introduced 15 new claims numbered 19-33.

New claim 19 finds support in claim 12 of the second preliminary amendment. The terms "allogenic" and "xenogenic" have been introduced into the claims based on the disclosure in line 9 of page 2 of the specification as filed. These terms are those understood by the skilled addressee as describing types of "heterologous" cells, as referred to in line 15 of page 4 of the specification, where an amendment has been made for consistency with the amended claims.

New claims 20-25 correspond to claims 13-18, respectively, of the second preliminary amendment.

Claim language for new claim 26 is derived from claim 6 as filed. Further claim language regarding the formation of the connective-tissue capsule is based on the disclosure in lines 30-32 of page 5 of the specification as filed. New claim 27 is a parallel claim to claim 18 of the second preliminary amendment. New claim 28 is derived from claim 6 as filed. New claims 29 and 30 correspond to claims 7 and 8, respectively, of the second preliminary amendment. New claims 31 and 32 are based on claim 10 of the second preliminary amendment. New claim 33 corresponds to claim 11 of the second preliminary amendment.

It is considered that the new claims satisfy the rejections of claims 1-9 (as originally filed) under 35 U.S.C § 112, second paragraph.

Claims 1-11, as originally filed, also stand rejected under 35 U.S.C § 112, first paragraph. Allegedly, given the state of the art which teaches against the use of polyacrylamide gel in view of its association with toxic substances, e.g. acrylamide monomers, it is not clear from the specification how such a gel could persist for a time in

vivo and not result in at least a non-specific inflammatory response.

In response, Applicants respectfully point out that the fundamental difference of the invention from known publications, including the references cited in the Office Action, is that the protective capsule is not produced in vitro and is not a simple polymeric structure, but comprises the connective tissue of the patient's own organism formed around introduced medical grade polyacrylamide gel.

None of the references cited disclose or even contemplate the use of a polyacrylamide gel as used in the present invention. One skilled in the art would not have expected that a polyacrylamide gel placed into a patient would make it possible to form a medium favorable for cultivating cells for a period of time sufficient for said cells to produce, for example, a biologically active substance, and that the polyacrylamide gel inside the formed connective-tissue capsule would prove a protection from immune effects of the host organism. The subject invention therefore is considered both surprising and unexpected.

Applicants also respectfully point out that, prior to the filing date of the application, it was known by those skilled in the art to employ polyacrylamide gel for medical purposes, such as for plastic surgery. In support, Applicants submit herewith a copy of a Russian Patent (RU 2127129) entitled PROCESS FOR PRODUCING A GEL-LIKE MATERIAL FOR SOFT TISSUES PLASTIC SURGERY, published before the filing date of the PCT application from which the present application claims priority. Also enclosed is an English language translation of relevant portions of the text of the Russian patent. The Examiner's attention is directed to the disclosure in the paragraph, common to pages 2 and 3 of the English translation regarding the purpose of the invention and to the disclosure in the second and third full paragraphs on page 4, the first full paragraph on page 7, the first full paragraph on page 8 and the first full paragraph on page 9 of the English translation, wherein the purity of the gel and the post-operative reactions of patients to the administration of the polyacrylamide gel are discussed.

Also provided are copies of the publications of the registered trademark associated

with the commercial name of the polyacrylamide gel employed (Bulletin 10 of the Russian Patent and Trademark Office, published May 25, 2000).

By submission of the enclosed proofs, the Applicants have met their burden in demonstrating that one skilled in the art would have been familiar with the medical grade polyacrylamide gel so that further description in the specification of this material should not be required. Such proof should satisfy both the enablement and written description requirements under 35 U.S.C § 112.

The title of the application has been amended to more clearly satisfy the provisions of 35 U.S.C § 112, since it is considered more descriptive of the invention being claimed.

A marked copy of the specification is provided on the attached separate page to assist the Examiner in following the amendments written into the specification.

It is believed that the rejections of the claims under 35 U.S.C § 112, first and second paragraphs have been met and that the application is in form for allowance.

Favorable consideration is respectfully requested.

A petition and fee for extension of time for one month also is enclosed.

Respectfully submitted,

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(54) PROCESS FOR PRODUCTION OF GEL-LIKE MATERIAL FOR SOFT TISSUES PLASTIC SURGERY

The invention relates to medicine and is intended for use in surgical practice for soft tissues plastic surgery.

Known in the art is application of a 3% polyacrylamide gel (USSR inventorship certificate N 1697756) for completing the volume of a vocal chord.

The main task whose solution is to be addressed by the invention, as being claimed and as set forth in the application resides in creating a material in the form of a gel on the basis of a copolymer of acrylamide that is useful as to its biological and physico-chemical properties for use as such for soft tissues plastic surgery.

The task set is to be solved owing to the fact that offered is a material in the form of a gel for soft tissues plastic surgery, comprising a polyacrylamide and a fluid medium, which according to the invention, comprises, as the polyacrylamide, a copolymer of acrylamide and methylene-bis-acrylamide in a ratio to mass of 100:0.5 - 5.0, the fluid medium is represented by weakly alkaline water, with a ratio of components, wt.%, as follows:

polyacrylamide	1.0 - 8.0
Water	92.0-99.0

and has a pH -value of 6.9 - 8.5, the level of permanganate oxidability not exceeding 1.0 mgO/l and the level of bromination ability not higher than 3.0 mgBr /l.

For the plastic surgery of hypodermic tissues, a gel-like material contains preferably the following ratio of components wt%:

polyacrylamide	I.5 - 2.5
water	97.5-98.5

For the plastic surgery of muscular and glandular tissues a material contains preferably the following ratio of components wt%:

polyacrylamide	4.0 - 8.0
water	92.0 - 96.0

The task set is further solved owing to the fact that claimed is a process for the preparation of a material for the plastic surgery of soft tissues in the form of a water-containing polyacrylamide gel, in which, according to the invention, the copolymerization of acrylamide is conducted with a methylene-bis-acrylamide in an aqueous medium at a pH of 9.0 - 9.5 in the presence of a peroxide polymerization initiator and, along with this, a reaction mixture is incubated at t = 20-90°C for 2 - 24 hours and then at t = 100-105°C for 2-4 hours.

The polymerization initiator used is represented by ammonium persulfate in an amount of from 0.0006 to 0.03 wt% or hydrogen peroxide in an amount of from 0.1 to 0.3 wt% or both components in any ratio in an amount not exceeding ones as mentioned hereinabove.

For the provision of a reaction mixture pH value, usable water is treated by an electrolysis method.

Now the invention will be described by way of graphic materials (Cf. the drawing) in which is shown the IR-spectrum of a gel material, as proposed, in the region of 4000 - 200 cm^{-1}.

The essence of the invention consists in that, firstly, experimentally selected are polymer-forming components and a quantitative ratio thereof; a fluid medium and the quantitative

ratio of the polymer with the fluid medium providing the density, as required, and material consistence; secondly, selected are conditions for obtaining a gel material which is useful as to its physico-chemical and biological properties for performing the plastic surgery of soft tissues.

The reaction of copolymerization of an acrylamide and a methylene-bis-acrylamide is known (USSR, Inventorship certificate N 1105767). In the process of polymerization there is formed a cross-linked polymer whose structure depends on synthesis conditions: the quantitative ratio of reagents, the qualitative composition of polymerization initiators and temperature conditions.

The claimed process on the account of a reaction mixture incubation in two steps - at lower temperatures first and then at higher temperatures - permits reducing the number of free amino groups (NH_2 radicals) in a polymer, which is corroborated by the graph presented in the drawing of the IR spectrum of the gel-like material as proposed (the material contains 5% of polyacrylamide, wherein 2 wt. parts of methylene-bis-acrylamide are for 100 wt. parts of acrylamide, and 95% of weakly alkaline water; a pH value of 8.0, the level of permanganate oxidability is 0.2 mgO/l, the level of bromination ability is 0.5 mg Br/l; it is obtained with incubation of an initial mixture at $t = 60^{\circ}C$ for 12 hours and then at $t = 100^{\circ}C$ for another 3 hours. As is evident from this spectrum, absent therein are bands of 1620 cm^{-1} responsible for the deformation vibrations of NH radicals and 3200 cm^{-1} and 3500 cm^{-1} responsible for stretching vibrations

of these radicals, which testifies to the fact that in the polymer structure, the contained free NH_2 radicals account for not more than I% of the total functional groups.

Besides this, pathomorphological research studies have shown (Cf. Report N 2 MMA) that the single-stage incubation of a reaction mixture results only at t=30-90°C or only at t= I00-I05°C in obtaining a gel having the level of permanganate oxidability of from 2.0 to 5.0 mgO/l and the level of bromination ability of from 3.0 to 5.0 mg Br/l. On administration of this gel into rats there were observed an inflammatory reaction and sclerosed tissues and also accelerated gel resorption.

The process, as disclosed, further permits eliminating a stage of washing off the resultant material from toxic initial monomers, since the concentration of initial components and polymerization process conditions enable one to obtain a gel devoid of the unreacted monomers, a factor that is confirmed by the test results of the target product.

The acrylamide and methylene-bis- acrylamide are taken suitable for biological purposes and not requiring further purification.

Water is purified by distilling it twice and , then subjected to electrolysis, as it is described in the "Methodic instructions on the preparation of electrochemical activated solutions (neutral analite) generated in an installation STEL-4M-60-0I for purposes of presterilization purification and sterilization", Moscow, I993.

A gel is produced in the following manner.

For the preparation of a reaction mixture, use is made of distilled-twice water subjected to electrolysis at the voltage

of 220 V, the current intensity of 6A, with a pH value after electrolysis treatment, of from 9.0 to 9.5. An aqueous solution of acrylamide and methylene-bis-acrylamide is prepared in a ratio to mass thereof being between 100:0.5-5.0 and, along with this, the total of the initial monomers in the solution is 1.0-8.0%. Gels with various density and elasticity are obtained by varying the amount of initial monomers in the mixture. The resultant solution is added with polymerization initiators: hydrogen peroxide in an amount of from 0.1 to 0.3 wt.% or ammonium persulfate in an amount of from 0.0006 to 0.03 wt.% or a mixture thereof in any ratio in an amount not exceeding the sum total of peak values thereof. The finished reaction mixture is filtered through bactericidal polymer filter means, brand F8273, with the pore size of 0.45 mm CA/CN, the manufacturer Sigma (USA), and is poured in nitrogen stream in glass containers in the required volumes. The containers are hermetically packed up and placed for incubation at t= 20-90°C for 2-24 hours followed by raising the temperature up to 100-105°C, and the incubation is carried out for another 2-4 hours.

With hydrogen peroxide being present in an incubation medium the latter turns into water and ozone which sterilizes the final product. However, for reliability's sake, the resultant gel is sterilized by autoclaving (t=120°C, p = 1,2 atm.) for 30 minutes.

The following characteristics of the obtainable material have been checked: an index of refraction (according to the methods described in the "Practical course in physical chemistry",

Moscow, I974, pp. 86-97);

a pH value, the level of permanganate oxidability - according to the methods contained in the book "Methodical instructions on sanitation-hygienic evaluation of rubber and latex products of medical designated purposes", Moscow, 1988, pp. 18, I9.

The level of bromination ability - according to the methods described in the "Collection of guide methodical materials for toxicological investigations of polymeric materials and products based thereon of medical purpose", Moscow, Ministry of Public Health of the USSR, 1987, pp. 27-29;

The content of the monomers of acrylamide and methylene-bis-acrylamide - according to the methods described in the "Collection of guide methodical materials on toxicological investigations of polymeric materials and products based thereon of medical purposes", Moscow, Ministry of Public Health of the USSR, I987, pp. 18-25.

The resultant material has the following physico-chemical characteristics:

Appearance	Colorless gel
Refractive index	1.328-1.360
Density	0.9 - 1.2 g/cm^3
pH	6.9 - 8.5
Acrylamide monomer content	absent
Methylene-bis-acrylamide monomer content	absent
Permanganate oxidability level	0.2-1.0 mgO/l
Bromination ability level	Not higher than 3.0 mgBr/l

The sanitation-chemical tests of the claimed material have been conducted in the Institute of Rubber-latex Products, toxicological and pathomorphological investigations - in the Moscow Medical academy named after I.M. Sechenov and in the All-Russia research institute for testing medical equipment under a program developed in the institute. As a result it has been established that the material proposed for soft tissues plastic surgery does not provoke tissue reaction, sensitization of organism, dystrophic and and necrotic changes; it is not mutagenous and is recommended for endoprosthesis and contour plastic surgery (Findings N 3, Report).

The resulting material has the following physico-chemical characteristics:

Appearance	Colorless gel
Refractive index	1.348
pH	7.2
Density	1.0 g/cm^3
Acrylamide monomer content	absent
Methylene-bis-acrylamide monomer content	absent
Permanganate oxidability level	0.4 mgO/l
Bromination ability level	0.1 mgBr/l

The resulting material has the following physico-chemical characteristics:

Appearance	Colorless gel
Refractive index	11.334
pH	8.3

Density	0.95 g/cm^3
Acrylamide monomer content	absent
Methylene-bis-acrylamide monomer content	absent
Permanganate oxidability level	10.6 mgO/l
Bromination ability level	0.15 mgBr/l

The material under consideration had been used for hypodermic tissue plastic surgery for removing wrinkles from the face. A gel was administered into patient S., aged 47.The operation was performed May 20, 1995. Postoperative observation 12 months with periodic examinations once in three months.No inflammatory and allergic symptoms. Patient's cosmetic effect was very good.

The resulting material has the following physico-chemical characteristics:

Appearance	Colorless gel
Refractive index	1.352
pH	8.0
Density	1.2 g/cm^3
Acrylamide monomer content	absent
Methylene-bis-acrylamide monomer content	absent
Permanganate oxidability level	0.2 mgO/l
Bromination ability level	0.05 mgBr/l

The resulting material was used for sural muscle plastic surgery. A gel, 150 g for a muscle, was implanted into patient S., aged 47.

The operation of administering the material proposed was carried out May 20, 1995. Postoperative period of observation 12 months with periodic examinations once in three months. The result: no inflammatory symptoms and edema observed.

According to the patient, a cosmetic effect was good.